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Review

Effect of Adjuvant Use of NSAID in Reducing Probing Pocket Depth in the Context of Conventional Periodontal Therapy: A Systematic Review of Randomized Trials

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Abstract: This systematic review aimed to assess the literature on the benefit of adjuvant nonsteroidal anti-inflammatory drugs (NSAIDs) during conventional periodontal therapy in terms of probing pocket depth (PD). A literature search according to PRISMA guidelines in Medline (PubMed), Embase (Ovid), and Cochrane library identified seven studies to be included in this review. In terms of the main outcome, PD, three studies found a larger reduction after NSAID administration compared to non-NSAID control patients. In two studies, no difference in PD reduction between NSAID and placebo was found. Overall, the NSAID patients showed no significant difference with an estimated 0.11 mm larger reduction in PD than the control [95% CI: −0.22 mm, 0.44 mm]. The secondary outcomes, bleeding on probing (BOP) and clinical attachment gain, also showed comparable results in all studies between patients receiving NSAID and those that did not. The estimated additional PD reduction of 0.11 mm in the NSAID group is very small and not statistically significant. It is unlikely that PD can be improved by adjuvant NSAID treatment after root surface debridement, yet the evidence to date is limited and warrants further investigation.

Keywords: periodontitis; non-surgical periodontal therapy; systematic review; nonsteroidal anti-inflammatory drugs

1. Introduction

Periodontitis is one of the major biological causes for adult tooth loss [1]. It represents an inflammatory disease triggered by biofilms and influenced by several environmental and systemic factors (e.g., stress, smoking, genetic susceptibility). An imbalance between bacterial attack and host response may cause an excessive inflammatory host reaction to plaque (PL) and lead to irreversible periodontal tissue damage [2,3]. Typical local signs of periodontal inflammation are edema and redness of the gingiva, bleeding on probing (BOP), pocket depth (PD) formation, and loss of clinical attachment (CAL). Finally, several studies have shown a relationship with diabetes [4,5], cardiovascular diseases [6,7], obesity [8,9], and pre-term delivery [10,11].

The major therapeutic goal is to positively influence the causative dysbiosis, mainly by debriding root surfaces and a modulation of risk factors, if existing. To mitigate excessive inflammatory host response, the use of adjuvant pharmacological substances has been suggested, such as non-steroidal

anti-inflammatory drugs (NSAIDs), which block proinflammatory pathways [12] and prevent tissue degradation.

NSAIDs have an analgesic, antipyretic, and antiphlogistic effect [13]. They block the enzyme cyclooxygenase (COX) and thus the synthesis of prostaglandins, which are involved in inflammatory processes and the development of pain and fever. Two types of cyclooxygenase are implied in different ways: COX-1 is constitutively expressed and is responsible for prostaglandin synthesis in the healthy organism, while COX-2 is mainly expressed in inflamed tissues. It is involved in physiological processes, such as cell proliferation and wound healing, and can be triggered very quickly in connection with inflammatory events. As a result, the intake of NSAIDs leads to pain relief and reduces inflammation [14].

However, taking NSAID can also lead to undesirable side effects, especially with long-term use. The prostaglandin synthesis takes place physiologically in many organs; the blocking of COX induces side effects in these areas, such as the stomach (prostaglandin E2—necessary for regulation of gastric acid), kidney (increases the glomerular filtration rate), encephalon, or platelets (thromboxane A2). Since the majority of side effects are caused by blocking COX-1, selective COX-2 inhibitors allow management of anti-inflammatory therapy with reduced side effects [15,16].

Already in the 1970s and 1980s, studies were undertaken that revealed that prostaglandins play a role in inflammatory processes and are relevant for the progression of periodontal disease [17,18]. Several studies have been conducted in animals and humans to demonstrate the positive effect of NSAIDs on reducing periodontal inflammation [19,20]. The group of non-steroidal anti-inflammatory drugs, especially COX-2 inhibitors, seems to be the most promising "host-modulating agents" to date [21].

Therefore, the purpose of this study was to systematically assess the effect of NSAIDs on periodontal inflammation when used as an adjunct to scaling and root planning (SRP). We hypothesized that the intake of NSAID, in combination with conventional periodontal therapy, leads to a reduced PD compared to placebo-controlled conventional therapy.

2. Materials and Methods

The review considered the PRISMA checklist [22] and the focused question applied the criteria of the PICO method [23]. The focused question of this systematic review was: "In patients with periodontitis, how does anti-inflammatory medication (NSAID) in conjunction with scaling and root planing affect PD as compared to scaling and root planing without medication?"

2.1. Literature Search Strategy and Study Selection

A systematic literature search was conducted and studies dating from 1958 to October 2018 were included. Studies were identified by searching the electronic databases Cochrane Library, Embase, Pubmed, and Medline. The reference lists of all included articles in order to identify possibly missed but cited papers were cross-checked. The search was limited to human subjects, clinical trials, and English and German language. The following MeSH terms were applied:

Population: periodontitis OR paradontitis OR parodontitis OR periodontal disease OR periodont OR parodont OR paradont OR pericemetitides OR pericementitis OR periodontitides OR periodontoses OR periodontosis;

Intervention: root planing OR dental scaling OR subgingival OR supragingival;

Comparison: with substances and synonyms.

Two reviewers (N.M., S.G.) independently screened titles and abstracts for inclusion. The same reviewers selected the full manuscript of those studies meeting the inclusion criteria. Any disagreement was resolved by discussion with a third reviewer (PRS (Appendix A).

2.2. Inclusion and Exclusion Criteria Screening and Selection

Abstracts were considered if the following inclusion criteria were fulfilled:

Population: patients with periodontitis.

Intervention: scaling and root planing with anti-inflammatory medication (NSAID).

Comparison: scaling and root planing without anti-inflammatory medication or placebo.

Outcome: recording and evaluation of PD.

Study design: Randomized controlled clinical trial with a minimum follow-up time of 10 days after scaling and root planing with or without anti-inflammatory medication.

Studies were excluded for the following reasons: animal studies, in vitro studies, case reports, commentaries, non-randomized controlled clinical trial study designs, and surgical periodontal therapy (Appendix B).

2.3. Outcome Measures

The primary outcome measure was PD reduction between baseline and follow-up, to assess the benefit of adjuvant use of NSAID vs. conventional periodontal therapy. In addition to this primary outcome, secondary parameter outcomes, such as BOP, attachment loss gain, and plaque index, were described.

2.4. Data Extraction

The following data for each study were extracted: number of subjects, type of NSAID medication (test), dose and duration of administered drug, study period, PD, CAL, BOP, and intervention. PD reduction was calculated as the difference between PD at baseline and at follow-up, respectively. Its standard deviation was conservatively estimated as the square root of the sum of the squared standard deviations at baseline and follow up. CAL gain and PI change were calculated analogously.

2.5. Data Analysis and Synthesis

Random effects meta-analyses were performed for the endpoints PD reduction and CAL gain to estimate the pooled effect of the NSAID treatment against placebo (mean differences) across the seven studies. The inverse variance method was used for pooling and the restricted maximum-likelihood estimator was used to assess between-study heterogeneity, expressed as I^2 index and tested with the Q statistic. The models were diagnosed using funnel, radial, and qq-plots and met modelling assumptions well. All analyses and plots were computed with the statistical software R [24], including the package metaphor [25]. The statistical significance level was set to $\alpha = 0.05$.

2.6. Assessment of Quality of Studies

The studies of interest were evaluated for quality with the Oxford quality scoring system by two authors (N.M. and S.G.) [26] (Appendix C).

3. Results

3.1. Study Selection

Initially, 556 studies were identified by an electronic data search. After reviewing the titles and abstracts, 22 potentially relevant studies were subjected to a full text evaluation. Of these, 15 studies were excluded based on their study design, research question, or missing numerical data for all the variables to be assessed in this study (PD, BOP, clinical attachment level, and plaque index), hence only seven studies with a detailed listing of such data could be included in the quantitative comparison (Figure 1).

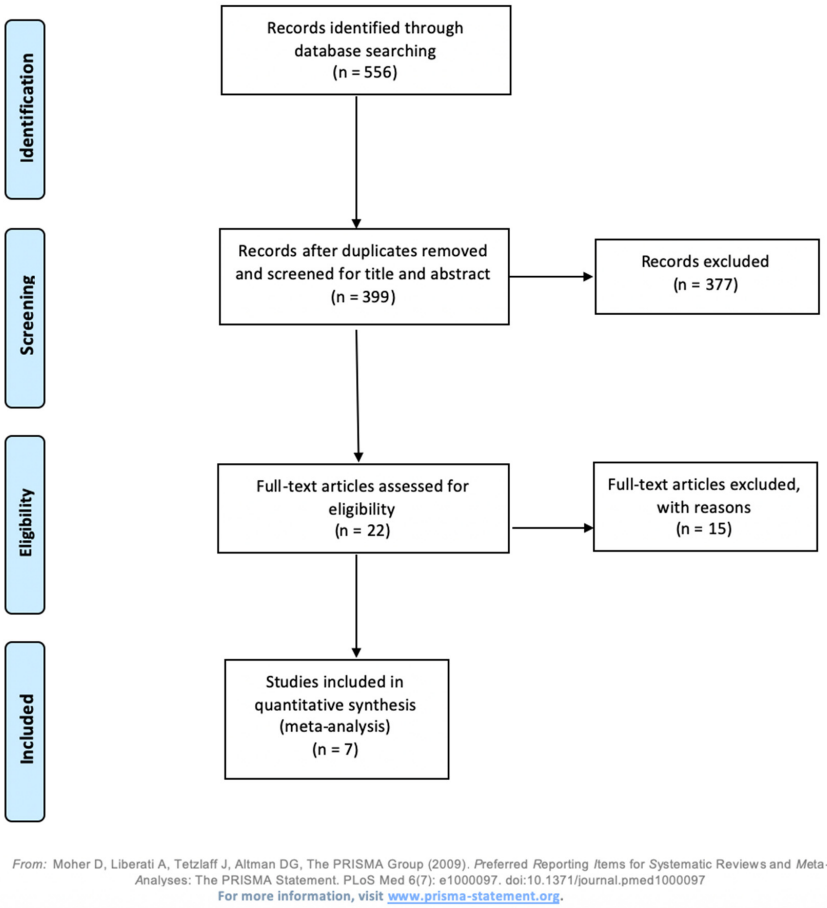


Figure 1. Prisma flow chart of the study selection process for this systematic review.

3.2. *Description of Characteristics*

The methodological characteristics of the selected studies are presented in Table 1. The study characteristics relevant to the specific research question are described as follows:

Population: Five of the studies included were performed in Turkey [27–31], one in Brazil [32], and one in the United States of America with mostly Caucasian followed by black subjects [33]. The study by Azoube et al. 2008 investigated patients with aggressive periodontitis [32]. All remaining studies included patients with chronic periodontitis [27–31,33]. All participants included in the study were systemically healthy, did not have hypersensitivity to NSAIDs, and were not pregnant or lactating. Four studies [27,28,30,32] excluded smokers from the study, whereas three studies [29,31,33] included smokers. Kurtis et al. not only included smokers but also divided smokers and non-smokers between the test and control group [29].

Overall, a total of 276 subjects were assessed in the meta-analysis. In detail, 135 subjects were assigned in the control group and received a placebo during scaling and root planing and 141 participants in the test group received an NSAID.

Intervention/Comparison: All studies except for Buduneli et al. gave oral hygiene instruction before or after the treatment. All participants in the studies received scaling and root planing with either an NSAID (test group) or a placebo (control group) [27–33]. The dose and duration of NSAID application varied between the studies depending on the length of the follow-up period. Patients were instructed to take either one or two tablets a day for 7 [32] or 10 [28–31] days. Aras et al. prescribed a six-week NSAID intake of one tablet a day and Yen et al. a six-month NSAID intake of one tablet a day. Study periods ranged from 4 weeks to 12 months and were categorized according to an early follow-up (7 days to 4 weeks) or a late follow-up (6 to 12 weeks) (Table 2).

Table 1. Characteristics of the included publications comparing nonsteroidal anti-inflammatory drugs (NSAID)f to placebo.

Study (Year)	Population Characteristics (Ethnicity, Age, Inclusion Criteria)	No. of Patients (m/f), Smoking Status	Study Design	Intervention (Test vs. Control)	Dose	Duration	Study Period	Analyzed Parameters
Aras, H. et al., 2007	• Ethnicity: Turkish • 18 to 54 years • Inclusion criteria: chronic periodontitis with min. of 20 natural teeth; • Exclusion criteria: pregnancy; smoking; systemic anti-microbial/anti-inflammatory drug therapy within 6 months before entry; periodontal treatment undertaken <6 months before the baseline visit; any systemic condition that might affect the progression or treatment of periodontitis;	34 (17/17); NS; CP	RCT	• Test (n = 17): SRP + OHI Naproxen Sodium • Control (n = 17): SRP + OHI Placebo • Clinical measures: day 0 and 6 weeks	275 mg	1x/d for 6 weeks	6 weeks	• GCF • PD • GI • PI • GBI
Azoubel, M.C. et al., 2008	• Ethnicity: Brazilian • 18 to 35 years • Inclusion criteria: ≥20 teeth and at least 4 sites in different teeth with PD ≥4 mm and 2 sites with PD ≥7 mm; • Exclusion criteria: hypersensitivity to NSAIDs; systemic conditions that modify the progression or treatment of periodontal diseases; diabetes and immunodeficiencies; antibiotic for periodontal procedures; periodontal treatment during the last 6 months; NSAIDs in the last 30 days or antibiotics in the last 60 days; use of drugs that interfere in the inflammatory response, immunologic system, or bone metabolism during the last 60 days; smoking; pregnancy and lactation; significant alteration in the hemogram or coagulogram; furcation involvement;	21 (2/19); NS; AP	RCT randomized, placebo-controlled, parallel-design, double-masked clinical trial	• Test (n = 11): SRP (40-min session per sextant) + Etoricoxib • Control (n = 10): SRP (40-min session per sextant) + Placebo • OHI before the therapy and weekly reinforcement; prophylaxis done weekly until the reassessment 30 days later. • Clinical measures: day 0, 7, and 30 days	120 mg	1x/d for 7 days	30 days	• PD • CAL • REC • PI • BOP • linear distance • gray levels • PGE_2
Buduneli, N. et al., 2010	• Ethnicity: Turkish • Test: mean age 48.4 (2.1) years Control: mean age 47.2 (1.9) years • Inclusion criteria: systemically healthy; CP with at least four sites CAL of ≥4 mm and PD of ≥5 mm, two in the anterior region; • Exclusion criteria: diabetes or other forms of systemic inflammatory diseases; systemic disease in which administration of meloxicam would be contraindicated; medicines likely to influence periodontal health; hypersensitive to NSAIDs; antibiotics/anti-inflammatory drugs or periodontal treatment within the last 3 months; pregnant or lactating women; smokers; fewer than 16 teeth at baseline of the study;	50 randomized; 40 analyzed; (20/20); NS; CP	RCT randomized, double-blind, placebo-controlled and parallel-design	• Test (n = 26); 6 discontinued study or lost to follow up): SRP + Meloxicam • Control (n = 24); 4 discontinued study or lost to follow up): SRP + Placebo • Clinical measures: day 0, 10 days, 4 weeks	7.5 mg	1x/d for 10 days	4 weeks	• PGE2 • IL-1β • CAL • PD • PI • PBI
Kurtis, B. et al., 2007	• Ethnicity: Turkish • Group 1: 39 to 55 years Group 2: 43 to 54 years Group 3: 42 to 55 years Group 4: 46 to 56 years • Inclusion criteria: CP at least six sites with >4 mm PD; and showing Radiographic evidence of bone and attachment loss in single rooted-teeth; good general health; • Exclusion criteria: periodontal therapy or medication during the past 6 months; history of systemic conditions, such as heart disease, diabetes mellitus, stomach or duodenal ulcer, or other types of disorders; medication that could affect manifestations of periodontal disease, such as chronic antibiotic use, phenytoin, cyclosporine, anti-inflammatory drugs, systemic corticosteroids, or calcium channel blockers; postmenopausal;	29 NS/29 smoker Group 1 (NSAID): 14 NS; CP (12/2) Group 2 (Placebo): 15 NS; CP (8/7) Group 3 (NSAID): 14 smoker; CP (10/4) Group 4 (Placebo): 15 smoker; CP (9/6) Smokers had smoked ≥10 cigarettes daily for >5 years. NS had never smoked.	NR	• Group 1 (n = 14): SRP + Flurbiprofen • Group 2 (n = 15): SRP + Placebo • Group 3 (n = 14): SRP + Flurbiprofen • Group 4 (n = 15): SRP + Placebo • OHI • Clinical measures: day 0 and 10 days	100 mg	2x/d for 10 days	10 days	• PI • GI • PD • CAL • GCF

Table 1. *Cont.*

Study (Year)	Population Characteristics (Ethnicity, Age, Inclusion Criteria)	No. of Patients (m/f), Smoking Status	Study Design	Intervention (Test vs. Control)	Dose	Duration	Study Period	Analyzed Parameters
Özgoren, Ö. et al., 2014	• Ethnicity: Turkish • Group 1: 31 to 57 years Group 2: 31 to 59 years • Inclusion criteria: CP at least 4 sites with PD of 4–6 mm; radiographic evidence of bone and attachment loss involving the maxiallary anterior teeth; • Exclusion criteria: systemic diseases where administration of NSAIDs are contraindicated; insulin dependent diabetes mellitus; known hypersensitivity to NSAIDs; pregnancy; smoking; any antibiotic; systemic corticosteroid, or immunosuppressive drug in the past 6 months;	32 Group 1: 16; NS; CP (9/7) Group 2: 16; NS; CP (9/7)	RCT randomized, double-blind, placebo-controlled	• Group 1 (n = 16): SRP + Tenoxicam • Group 2 (n = 16): SRP + Placebo • OHI • Clinical measures: day 0 and 30 days	20 mg	1x/d for 10 days	30 days	• PI • GI • GBI • PD • CAL • MMP-8 • TNF-α
Vardar, S. et al., 2003	• Ethnicity: Turkish • 35 to 59 years • Inclusion criteria: at least two teeth in each quadrant with PD ≥ 5 mm and CAL ≥ 4 mm, and a minimum of 18 natural teeth; • Exclusion criteria: systemic diseases; pregnancy or nursing mothers; stomach or duodenal ulcer; allergy to aspirin or NSAIDs; any anti-inflammatory drug within the past month, or any antibiotic, systemic corticosteroid, or immune-suppressive drug within the past 3 months;	30 (17/13); (1) nimesulide (3/7) smokers/NS; (2) naproxen (5/7) smokers/NS; (3) Placebo group (3/7) smokers/NS; CP; (4) Control (3/7) smokers/NS; healthy	RCT double-blind placebo controlled	(1) SRP + nimesulide; (n = 10) (2) SRP + naproxen; (n = 12) (3) SRP + placebo (n = 10) (4) Control (n = 10) • OHI • Clinical measures: 0, 10 days and 3 months	nimesulide 100 mg naproxen; 275 mg	2x/d for 10 days	3 months	• PI • PBI • PD • CAL
Yen, C.A. et al., 2008	• Ethnicity: USA (64 White, 24 Black, 4 Hispanic, 7 Asian, 2 other) • 18 to 75 years • Inclusion criteria: minimum of 16 teeth, at least two of which were molars; at least four teeth PDs > 4 mm; loss of attachment > 2 mm; minimum of two interproximal areas with radio-graphic evidence of bone loss; • Exclusion criteria: periodontal therapy in the past 12 months; extensive use of aspirin or NSAIDs within 12 months; history of antibiotic therapy in the past 6 months; any condition that would require antibiotic premedication for prevention of subacute infective endocarditis; hypersensitivity to celecoxib or other COX-2 inhibitors, aspirin, or NSAIDs; history of radiation therapy in the head and neck area; history of Sjögren's syndrome; history of peptic ulcers or any other condition that would be a contraindication for the use of NSAIDs or COX-2 inhibitors (aspirin/NSAID-induced asthma or urticaria, aspirin triad, hepatic failure, sulfa drug allergy, pregnancy, labor and delivery, and nursing)	131 (54 male); CP; smoker/NS/Ex-smoker (40/35/24) 101 (54 celecoxib/ 47 placebo) returned for 3-month follow-up; 85 (45 celecoxib/ 40 placebo) returned for 6-month visit; 74 (40 celecoxib/ 34 placebo) returned for 9-month visit; 65 (35 celecoxib/ 30 placebo) completed 1-year study	RCT double-masked, randomized, placebo-controlled clinical trial	• Test (n = 54): SRP + Celecoxib • Control (n= 47): SRP + Placebo • OHI • Clinical measures: • 0, 3, 6, 9, 12 months	200 mg	1x/d for 6 months	12 months	• CAL • PD • % CAL loss/gain ≥2mm • BOP • PI • Mobility • tooth sites: shallow, moderate or deep

AP—aggressive periodontitis, CAL—clinical attachment level, CP—chronic periodontitis, GCF—gingival crevicular fluid, GBI—gingival bleeding index, GI—gingival index, NR—not reported, NS—non-smoker, OHI—oral hygiene instruction, PD—probing pocket depth, PL—plaque index, RCT—randomized controlled clinical trial, SRP—scaling & root planning.

Table 2. NSAID dose and duration of follow-up in studies included in the quantitative assessment.

Study	NSAID	Dose	Duration	Max. Dose/d
Early follow-up: 7 d–4 wks				
Azoubel et al., 2008	Etoricoxib	120 mg	1x/d, 7 d	120 mg (max 8 d)
Buduneli et al., 2010	Meloxicam	7.5 mg	1x/d, 10 d	15 mg
Kurtis et al., 2007	Flurbiprofen	100 mg	2x/d, 10 d	300 mg
Özgoren et al., 2014	Tenoxicam	20 mg	1x/d, 10 d	40 mg
Late follow-up: 6–12 wks				
Aras et al., 2007	Naproxen Sodium	275 mg	1x/d, 6 wks	600 mg 1250 mg (prescription)
Vardar et al., 2003	Nimesulide	100 mg	2x/d, 10 d	200 mg (max 15 d)
	Naproxen	275 mg	2x/d, 10 d	s.o.
Yen et al., 2008	Celecoxib	200 mg	1x/d, 6 mths	400 mg

Outcome: All studies recorded PD, PI, and some method of gingiva inflammation recording (BOP, PBI, GBI) at baseline, different follow-up intervals, and at the final examination. Kurtis et al. took measurements at the beginning and 10 days after the intervention as a final recording of the study, so that it represented the shortest follow-up time [29]. Yen et al. distinguished PD recordings between moderate and deep pockets. Six out of seven studies documented CAL [28–33]. Some studies examined gingival crevicular fluid (GCF) [27,29] and prostaglandin E_2 (PGE_2) [28,32]. Buduneli et al. studied interleukin-1-beta (IL-1b) levels whereas Özgören et al. investigated levels of MMP-8 and TNF-α in subjects with chronic periodontitis.

Study design: All studies included a control group, which used a placebo. Five controlled clinical trials were double blinded [28,30–33].

3.3. Primary Outcome of the Intervention on Probing Pocket Depth (PD) Reduction

All seven studies assessed the PD at baseline and at the endpoint. The frequency of follow-up assessments varied from one to four follow-up appointments. Re-evaluation took place after 10 days, 4 weeks, or 12 weeks. Studies with the same follow-up period are compared in Table 3.

Table 3. Probing pocket depth in comparison to non-NSAID and NSAID groups at three different follow-up timepoints.

Study and Groups	Non-NSAID (*n*)	NSAID (*n*)	ΔPD in mm Non-NSAID (SD)	ΔPD in mm NSAID (SD)	Dose (%)
10 day-follow-up					
Buduneli et al., 2010	20	20	−1.30 (1.42)	−1.60 (1.13)	50
Kurtis et al., 2007	/	/	/	/	33.3
smokers	15	14	−0.01 (0.50)	0.01 (1.51)	
non-smokers	15	14	−0.01 (0.62)	0.01 (1.21)	
4 week/30 days-follow-up					
Buduneli et al., 2010	20	20	−1.90 (1.48)	−2.80 (1.20)	50
Azoubel et al., 2008	10	10	−2.48 (0.99)	−2.17 (0.44)	100
Özgoren et al., 2014	16	16	−0.72 (0.77)	−0.72 (0.64)	50
12 week-follow-up					
Vardar et al., 2003	10		−4.1 (1.39)		
Nimesulide		10		−3.25 (1.09)	50
Naproxen		10		−4.45 (1.33)	137.5
Yen et al., 2008	47	54			50
moderate pockets			−0.98 (6.17)	−1.14 (6.76)	
deep pockets			−1.89 (10.97)	−3.27 (11.46)	

Buduneli et al. [28] compared 20 patients that received NSAIDs with 20 non-NSAID patients in the control group. The reduction in PD was 1.3 mm in the control group and 1.6 mm in the NSAID group after 10 days, whereas the reduction of PD was much less after 30 days. Kurtis el. al [29] divided the control and NSAID groups further into smokers and non-smokers, with 15 patients in each non-NSAID group and 14 patients in each NSAID group. Only minimal changes of ±0.01 mm were observed, where both the smokers and non-smokers in the non-NSAID group showed an increase in PD of 0.01 mm while the non-smokers in the NSAID group achieved a reduction of 0.01 mm in PD. At four weeks of follow-up, two studies demonstrated only moderate or no differences in the probing pocket depth between the non-NSAID and NSAID groups. Azoubel et al. [32] showed an average reduction of 2.48 mm (SD 0.99 mm) in the control group compared to 2.17 mm (SD 0.44) in the NSAID group, while Özgören et al. [30] found the exact same average reduction of 0.72 mm (SD non-NSAID: 0.77; SD NSAID: 0.64) in both groups. Vardar et al. [31] analyzed 3 groups of 10 patients each, either receiving placebo (control group), Nimesulide, or Naproxen (test group). At the 12-week follow-up, the control group had a PD decrease of 4.1 mm (SD 1.39 mm), while PD decreased by 3.25 mm (SD 1.09 mm) in the Nimesulide group and by 4.45 mm (SD 1.33) in the Naproxen group. Yen et al. [33] observed differences in the reduction of the PD in cases with deep pockets, where the NSAID group showed a reduction of 3.27 mm (SD 11.46 mm) compared to 1.89 mm (10.97 mm) in the control group at the 12-week follow-up. The reduction of the probing depth in patients with moderate pockets was comparable between the NSAID group (1.14 mm reduction, SD 6.76 mm) and the non-NSAID control group (0.98 mm reduction, SD 6.17 mm).

Numerical data from seven studies were quantitatively evaluated to compare PD reduction between the NSAID intervention group and the control group. The data are presented graphically in Figure 2 to show the differences between the studies and the study groups.

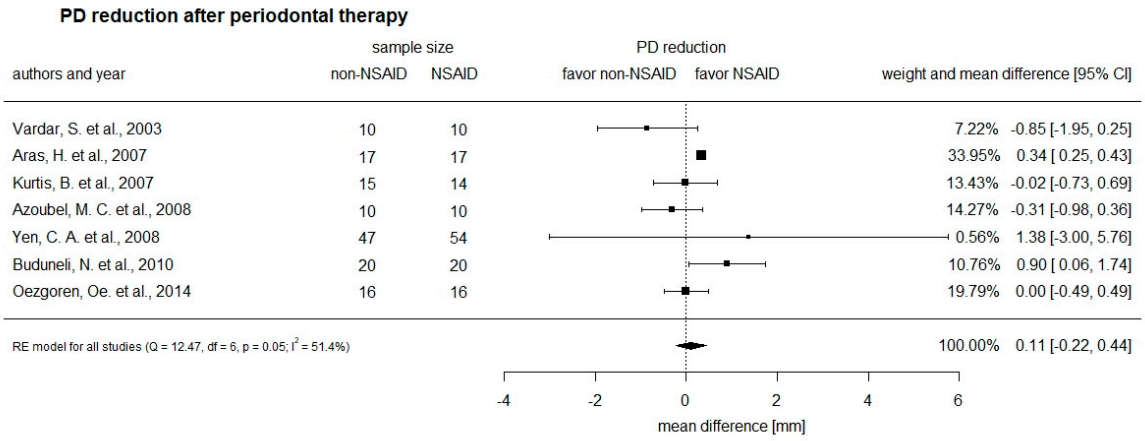


Figure 2. Forest plot comparing probing pocket depth (PD) reduction between non-NSAID and NSAID groups.

The study by Kurtis et al. [29] collected data on smokers, while all other studies investigated only non-smokers. Three of the seven studies evaluated showed a larger PD reduction in the NSAID-treated group compared to the non-NSAID control group. Two studies showed a similar PD reduction for both the control and the NSAID groups. Two studies found a larger PD reduction in the control group with patients that had not received NSAID compared to those that did. The overall calculated difference in PD reduction was 0.11 mm [95% confidence interval −0.22 mm; 0.44 mm] greater in the NSAID group than the non-NSAID group. Kurtis et al. [29] was the study with the shortest follow-up time, showing similar results compared to the other studies and proving to be both neither significant nor clinically relevant.

3.4. Secondary Outcome of the Intervention on Bleeding on Probing (BOP)

Five studies presented quantitative data on BOP at three different follow-up timepoints (Table 4). Budunelli et al. [28] re-evaluated BOP using the papilla bleeding index (PBI) in 20 non-NSAID and 20 NSAID patients and found a comparable reduction of the index in both groups (non-NSAID: 1.6 SD 0.99; NSAID: 1.5 SD 1.13). Kurtis et al. [34] categorized the patients according to their smoking status and found a reduction in BOP reflected by the gingival index (GI) of 1.5 (SD 0.41) in non-NSAID smokers and 1.6 (SD 0.16) in non-NSAID non-smokers, while the reduction in the NSAID group was smaller, with 1.32 (SD 0.40) in smokers and 1.28 (0.69) in non-smokers. Two studies assessed bleeding on probing after four weeks of follow-up, yet both studies are difficult to compare as Azoubel et al. [32] reported the relative BOP as a percentage, while Özgören et al. used the GI to assess this parameter. Of the two studies with a patient re-evaluation after 12 weeks, only the study by Vardar et al. [31] reported results on BOP, which was reduced by 1.85 (SD 1.28) in the non-NSAID group and by 2.1 (SD 1.00) and 1.85 (SD 1.13) in the Nimesulide and Naproxen groups, respectively, based on the PBI. Overall, all studies report no significant difference in BOP among the NSAID and the non-NAID group.

Table 4. Bleeding on probing (BOP) in comparison to non-NSAID and NSAID groups at three different follow-up timepoints.

Study and Groups	Non-NSAID (*n*)	NSAID (*n*)	ΔBOP in mm Non-NSAID (SD)	ΔBOP in mm NSAID (SD)	Dose (%)
10 day-follow-up					
Buduneli et al., 2010	20	20	−1.60 (0.99)	−1.50 (1.13)	50
Kurtis et al. 2007					33.3
smokers	15	14	−1.50 (0.41)	−1.32 (0.40)	
non-smokers	15	14	−1.60 (0.16)	−1.28 (0.69)	
4 week/30 days-follow-up					
Buduneli et al., 2010	20	20	−1.8 (0.76)	−2.1 (0.89)	50
Azoubel et al., 2008	10	10	−47.58% (22.01)	−57.44% (15.43)	100
Özgoren et al., 2014	16	16	−0.53 (0.37)	−0.59 (0.29)	50
12 week-follow-up					
Vardar et al., 2003	10		−1.85 (1.28)		
Nimesulide		10		−2.10 (1.00)	50
Naproxen		10		−1.85 (1.13)	137.5

3.5. Secondary Outcome of the Intervention on Clinical Attachment Gain (CAL)

In total, 4 of the 12 included studies did not assess the CAL gain, and 2 studies that did assess this parameter did not present numerical data, leaving 6 studies for a quantitative comparison of this parameter. The frequency of follow-up assessments varied from one to four follow-up appointments. Studies with the same follow-up period of 10 days, 4 weeks, or 12 weeks are compared in Table 5.

Two studies evaluated the patients 10 days after the initiation of NSAID treatment. Buduneli et al. [28] reported a gain in CAL by 0.5 mm (SD 1.98 mm) in the non-NSAID group compared to 1.2 mm (SD 2.13 mm) in the NSAID group after 10 days and greater after 30 days. Kurtis et al. [29] observed a gain of 0.29 mm (SD 0.51) in the CAL in the smoking non-NSAID group, while the non-smoker control group showed a clinical attachment gain of 0.01 mm (SD 1.16). In contrast, the non-smokers of the NSAID group showed no difference in CAL gain compared to the smokers in this group with 0.01 mm (SD 1.5).

At four weeks of follow-up, the observed CAL was comparable between the non-NSAID group and the NSAID group in the two studies with a re-evaluation at this timepoint. Azoubel et al. [32] reported a CAL gain of 2.23 mm (SD 1.36 mm) in the control group compared to 1.95 mm (SD 0.71) in the NSAID group, while Özgören et al. [30] observed only minimal changes in this parameter four weeks after initiation of the treatment, with a gain in CAL of 0.009 mm (SD 1.02 mm) and on average

no change in the NSAID group (SD 1.27). Two studies evaluated the CAL after a follow-up period of 12 weeks. Vardar et al. [31] reported a gain in CAL for all three groups (placebo/non-NSAID group, Nimesulide, or Naproxen) of 1.3, 1.35, and 1.15 mm, respectively. Yen et al. [33] found the highest gain in CAL in the NSAID group with deep PD at 3.04 mm (SD 11.83 mm). The control group with deep PD showed an average gain of 1.46 mm (SD 12.82). The gain of the CAL in patients with moderate pockets was comparable between the NSAID-group (−1.06 mm, SD 7.42 mm) and the non-NSAID control group (−0.83 mm, SD 7.42 mm).

Table 5. Clinical attachment level in comparison of non-NSAID and NSAID groups at three different follow-up timepoints.

Study and Groups	Non-NSAID (*n*)	NSAID (*n*)	ΔCAL in mm Non-NSAID (SD)	ΔCAL in mm NSAID (SD)	Dose (%)
10 day-follow-up					
Buduneli et al., 2010	20	20	−0.50 (1.98)	−1.20 (2.13)	50
Kurtis et al.,2007					33.3
smokers	15	14	0.29 (0.51)	0.01 (1.50)	
non-smokers	15	14	0.01 (1.16)	0.01 (1.31)	
4 week/30 days-follow-up					
Buduneli et al., 2010	20	20	−1.20 (1.91)	−1.50 (2.00)	50
Azoubel et al., 2008	10	10	−2.23 (1.36)	−1.95 (0.71)	100
Özgoren et al., 2014	16	16	−0.009 (1.02)	0.00 (1.27)	50
12 week-follow-up					
Vardar et al., 2003	10		−1.3 (1.62)		
Nimesulide		10		−1.35 (1.59)	50
Naproxen		10		−1.15 (2.02)	137.5
Yen et al., 2008	47	54			50
moderate pockets			−0.83 (7.54)	−1.06 (7.42)	
deep pockets			−1.46 (12.82)	−3.04 (11.83)	

Numerical data from six studies could be quantitatively evaluated for the CAL between the NSAID and control groups. The data are plotted in Figure 3 to demonstrate the observed gain in CAL in these six studies. Three of the six evaluated studies showed close to no difference in the average clinical attachment gain between the non-NSAID and NSAIFD groups. In one study, the clinical attachment gain was slightly larger in the control group compared to the NSAID group (mean difference: −0.28, confidence interval −1.23, 0.67), while in another study the opposite was observed with a slightly larger gain in CAL in the NSAID group compared to the control (mean difference: 0.30, confidence interval −0.92, 1.52). Only one study reported a larger CAL gain in the NSAID group than in the control group (mean difference: 1.58, confidence interval −3.26, 6.42).

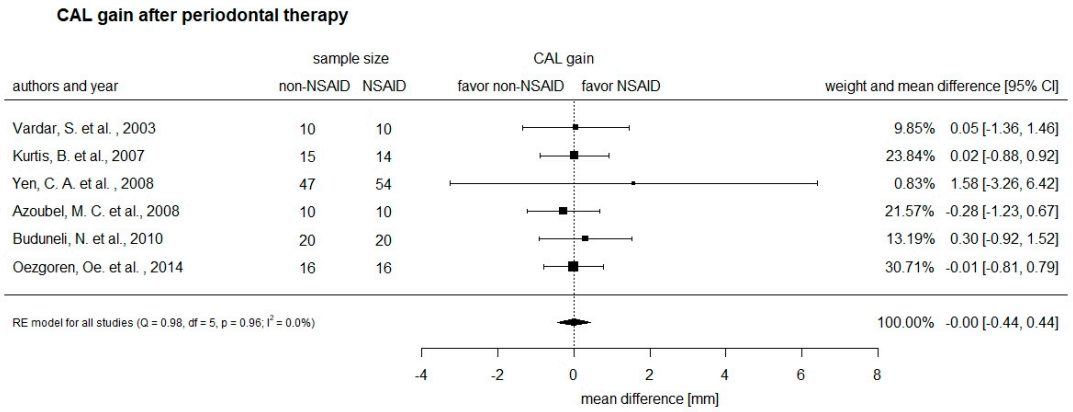


Figure 3. Forest plot comparing clinical attachment (CAL) gain between non-NSAID and NSAID groups.

3.6. Secondary Outcome of the Intervention on Plaque Index (PI)

The results of the seven studies are listed in Table 6. Unfortunately, the results of these studies are not directly comparable, because the PI was assessed at different follow-up timepoints and, importantly, different indices were used to assess the index. Looking at the studies individually, only one of the studies (Aras et al.) showed twice the reduction in the plaque index in the NSAID group than that determined for the non-NSAID groups [27]. In the other six studies, the indices were comparable between patients receiving NSAID and those who did not.

Table 6. Plaque index in comparison of non-NSAID and NSAID groups.

Study and Groups	Non-NSAID (*n*)	NSAID (*n*)	ΔPI Non-NSAID (SD)	ΔPI NSAID (SD)	Follow-up	Max. Dose/Day (%)
Aras et al., 2007	17	17	−0.7 (0.23)	−1.41 (0.18)	6 weeks	46
Azoubel et al., 2008	10	10	−65.82 (12.9)	−57.83 (20.2)	30 days	100
Buduneli et al., 2010	20	20	−74 (12.2)	−74 (34.9)	10 days	50
			−71 (11.2)	−64 (35.8)	4 weeks	
Kurtis et al., 2007	15	14	−1.48 (0.29)	−1.3 (0.53)	10 days	33.3
Özgoren et al., 2014	16	16	−0.79 (0.57)	−0.82 (0.56)	4 weeks	50
Vardar et al., 2003	10	10	−0.75 (0.12)	−0.7 (0.35)	12 weeks	50
Yen et al., 2008	47	54	−18.6 (25.0)	−20.9 (27.4)	12 weeks	50

4. Discussion

Periodontitis may result in a dysbiosis of the biofilm and host, eventually causing inflammation and destruction of periodontal tissues [34,35]. The conventional treatment of periodontitis entails root surface debridement to allow for a recovery of the symbiosis between the host and the oral microbiome [36,37]. This therapy may be supported by pharmacological treatment of the inflammation using NSAID. The aim of the present study was to assess the evidence for the benefits of such an adjuvant pharmacological therapy in the literature in terms of PD and the secondary parameters CAL level, PI, and BOP.

Twelve studies were initially identified and further assessed in terms of their suitability and quality. Seven studies met the inclusion criteria and provided numerical data on at least the main outcome parameter, PD.

The results of this systematic review showed that in two of the seven included studies, there was a significant reduction of PD with adjunctive NSAID treatment than with just conventional scaling and root planing. In two studies, the opposite was the case, where PD showed a larger reduction in the control group than in the NSAID group, while for two studies, the changes in PD were comparable. However, taking the data from these seven studies together, there were no significant differences in terms of the PD reduction between patients who received NSAID and those that did not. Overall, the reduction in PD was only 0.11 mm larger in the NSAID group compared to the controls. The largest average reduction was observed in the study by Yen et al. [33], with a 1.38 mm greater PD reduction in the NSAID group compared to the control group. Nonetheless, the PD reduction also showed the widest range in this study, with an estimated 95% confidence interval of −3.00 to 5.76 mm, indicating that there were large differences between the patients. The studies assessed the probing pocket depth at three different follow-up timepoints: 10 days, 4 weeks, and 12 weeks. This extended time span could have an impact on the PD results, as one might expect a larger reduction after a longer time-period and hence a longer intake of NSAIDs. Nonetheless, there were no obvious differences or trends between these different follow-up periods. In fact, the study by Buduneli et al. [28] with a follow-up period of only 10 days found a larger reduction of the PD in the NSAID group, while the study by Vadar et al. [31], assessing patients after a 12-week follow-up period, found a larger reduction in the control group. A systematic review published by Donos et al. [38] investigated the adjunctive use of host modulators in non-surgical periodontal therapy. Among drugs, such as bisphosphonate, sub-antimicrobial doxycycline, and probiotics, NSAIDs applied locally and systemically were evaluated. Due to the heterogeneity of the NSAIDs being used and dosage no metanalysis was directed.

The secondary parameters were not assessed in all seven studies, with BOP reported in five studies and CAL gain in six studies. NSAID intake did not appear to have an impact on BOP, as the differences at the follow-up timepoints compared to baseline were comparable between the NSAID and control groups in the five studies. The same was true for the CAL gain, which showed no difference between patients that received NSAID adjuvant therapy and those that did not.

The quality of the initially identified 12 studies was assessed using the Oxford quality scoring system. Three of the seven studies reviewed, Yen et al. [33], Azoubel et al. [32], and Bunduneli et al. [28], received the highest scores, not addressing randomization, blinding, and drop-out rate. Two of these studies, those authored by Yen et al. [33] and Bunduneli et al. [28], observed an impact of adjuvant NSAID use on PD reduction and CAL gain, while the study by Azoubel et al. [32] saw a larger improvement of these parameters in the control group. The other four studies scored comparatively low, with scores ranging from zero to three. Nonetheless, the Oxford quality scoring system is only one of such systems and does not consider factors, such as the clear formulation of a research question and the risk of bias.

The present systematic review has several limitations that may explain the results and should be addressed. First of all, seven studies with relatively few patients could be identified that met all the inclusion criteria, and therefore the numerical data for a statistical comparison was limited. The low number of suitable studies also meant that in order to quantitatively assess differences between NSAID and non-NSAID patients, the results of all seven studies had to be pooled for this comparison independent of the timepoint at which the assessment took place. It is therefore difficult to directly compare the results, as there were only two studies available for each timepoint and parameter. Furthermore, the type, dose, and duration of administration of the NSAID may have an impact on the outcome, yet the patients in the seven studies took different NSAIDs (Etoricoxib, Meloxicam, Flurbiprofen, Tenoxicam, Naproxen, Nimesulide, Celexocib) at different dosages (7.5–325 mg). It therefore remains unclear whether the impact of NSAID administration may have been more pronounced if the same duration of the follow-up timepoint and the same NSAID with the same dosage would have been compared.

5. Conclusions

The present study evaluated the evidence of NSAID adjuvant to scaling and root planing in the treatment of periodontitis. Only a few studies could be identified in the literature addressing this topic, of which a maximum of seven studies could be used to quantitatively assess the main and secondary outcomes. Of these, only three studies showed an improvement in the main outcome parameter, probing pocket depth, in patients receiving NSAIDs compared to those that did not. Overall, the data presented indicate that NSAID has no quantifiable beneficial effect as an adjunct to scaling and root planing. Future studies with a larger number of patients, standardized follow-up periods, as well as NSAID types and dosages are required to assess the suitability of NSAID as an adjuvant therapy in root surface debridement.

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Appendix A

Table A1. Pubmed Search Strategy.

Step	Query	Hits
1	(periodontal diseases/or exp periodontitis/or ((periodont* or parodont* or paradont*) adj3 (disease* or loss or pocket* or abscess*)).ti,ab. or (pericementitides or pericementitis or periodontitides or periodontitis or periodontoses or periodontosis or paradontitis or parodontitis).ti,ab.) not (animals not humans).sh.	58,306
2	Dental Scaling/or "Root Planing"/or periodontal diseases/th, dt or exp periodontitis/th, dt or ((dental or root or subgingival or supragingival) adj3 scaling*).ti,ab. or (root adj3 (planing* or planning*)).ti,ab. or ((periodont* or parodont* or paradont* or pericement*) adj5 (treat* or therap*)).ti,ab.	23,330
3	exp anti-inflammatory agents, non-steroidal/or exp cyclooxygenase 2 inhibitors/or ((anti-inflammatory or antiinflammatory) adj3 (agents* or drug* or therapy)).ti,ab. or ((COX-2 or cyclooxygenase-2) adj3 inhibitor*).ti,ab. or "systemic chemotherapeutic*".ti,ab. or (NSAID* or aspirin or "acetylsalicylic acid" or acetysal or acylpyrin or aloxiprimum or colfarit or dispril or easprin or ecotrin or endosprin or magnecyl or micristin or polopirin or polopiryna or solprin or solupsan or zorprin or ibuprofen or brufen or ip-82 or ip82 or ibumetin or motrin or nuprin or rufen or salprofen or dolgit or traumadolgit or flubiprofen or ansaid or cebutid or dobrofen or flugalin or flurbiprofen or fluriproben or froben or neo-artrol or novo-flurprofen or nu-flurbiprofen or ocufen or ocuflur or strefen or ratio-flurbiprofen or meloxicam or acticam or aflamid or artrilox or contacera or dormelox or ecax or emdocam or exel or flexicam or flodin or hexaphlogin or inflacam or loxibest or loxicam or loxicom or masflex or mecox or mel-od or melcox or melicam or melocam or melocox or melosolute or melosteral or melosus or melovem or melox or meloxidolor or meloxidyl or meloxin or meloxivet or meloxoral or merapiran or mesoxicam or metacam or mevamox or mexpharm or miloxam or mobec or mobic or mobicox or mopik or movalis or movatec or movi-cox or movicox or mowin or muvera or novem or ostelox or parocin or rafree or recocam or revitacam or rheumocam or rumonal or vivlodex or tenoxicam or alganex or arthrinal or aspagin or doxican or hobaticam or indo bros or indobros or istotosal or liman or mobiflex or neo endusix or neoendusix or octiveran or oxytel or palitenox or reutenox or "ro 12 0068" or soral or tenalgin or tilatil or tilcitin or tilconox or tilcotil or toscacalm or indomethacin or amuno or indocid or indocin or indomet-140 or indometacin or metindol or osmosin or alrheumat or alrheumum or benzoylhydratropic-acid or ketoprofen or orudis or profenid or ketorolac or rs-37619 or rs37619 or naproxen or aleve or anaprox or methoxypropiocin or naprosin or naprosyn or naproxenate or proxen or synflex or etoricoxib or acoxxel or algix or arcoxia or auxib or bericox or caretor or coxerit or coxeta or coxient or coxiloc or coxitor or coxolin or doloxib or ecoxyton or etori or etoriax or etorican or etoricox or "etoricoxib hydrochloride" or etorikoksib or etorilin or etoxib or evetore or exinef or exxiv or halliztolva or imesol or itoroxx or kostarox or l-791456 or l791456 or linzavo or mk-0663 or mk-663 or mk0663 or mk663 or narox or nucoxia or oxidraxib or roticox or tauxib or turox or celecoxib or celebrex or sc-58635 or sc58635).ti,ab.	250,911
4	1 and 2 and 3	361
5	Periodontal Index/or ((periodontal or parodont* or paradont* or pericement* or gingival) adj3 (index or indices or indexes or status)).ti,ab. or (bleeding* or pocket*).ti,ab.	236,334
6	4 and 5	101
7	("18771374" or "22092475" or "23594239" or "18166099" or "19180322").ui.	5
8	6 and 7	5
9	4 not 6	260

Appendix B

Table A2. Excluded studies.

Excluded Studies	Reason for Exclusion
O. Aboul-Dahab, A clinical evaluation of non-steroidal anti-inflammatory drugs (NSAIDS) as adjuncts in the management of periodontal disease, Egypt Dent J 39(3) (1993) 511-8.	No full text available
N.C. Deshpande, K.M. Bhat, G.S. Bhat, A.N. Deshpande, Randomized, controlled clinical study to evaluate efficacy of novel indigenously designed controlled release flurbiprofen gel system for management of periodontal diseases, Contemp Clin Dent 4(1) (2013) 32–6.	Primary outcome (PD) not investigated
H. El-Sharkawy, N. Aboelsaad, M. Eliwa, M. Darweesh, M. Alshahat, A. Kantarci, H. Hasturk, T.E. Van Dyke, Adjunctive treatment of chronic periodontitis with daily dietary supplementation with omega-3 Fatty acids and low-dose aspirin, Journal of periodontology 81(11) (2010) 1635–43.	Not addressing research question
N.M. Elwakeel, H.H. Hazaa, Effect of omega 3 fatty acids plus low-dose aspirin on both clinical and biochemical profiles of patients with chronic periodontitis and type 2 diabetes: a randomized double-blind placebo-controlled study, Journal of periodontal research 50(6) (2015) 721–9.	Not addressing research question
T.F. Flemmig, B. Epp, Z. Funkenhauser, M.G. Newman, K.S. Kornman, I. Haubitz, B. Klaiber, Adjunctive supragingival irrigation with acetylsalicylic acid in periodontal supportive therapy, Journal of clinical periodontology 22(6) (1995) 427–33.	Not addressing research question
E. Funosas, G. Feser, L. Escovich, L. Maestri, Alteration of hemostasis in patients treated with subgingival NSAIDs during periodontal therapy, Acta Odontol Latinoam 25(1) (2012) 103-8.	Not addressing research question
E.R. Funosas, L. Escovich, L. Maestri, The use of topical subgingival gels of non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to non-surgical management of chronic periodontitis, Acta Odontol Latinoam 22(3) (2009) 215–9.	No full text available
P.A. Heasman, D.K. Benn, P.J. Kelly, R.A. Seymour, D. Aitken, The use of topical flurbiprofen as an adjunct to non-surgical management of periodontal disease, Journal of clinical periodontology 20(6) (1993) 457–64.	Not addressing research question
NCT02149758, Effect of selective COX-2 Inhibitor (Etoricoxib) along with SRP on clinical parameters and salivary level of superoxide dismutase in chronic generalized periodontitis a double-blind, placebo-controlled, double-masked randomized controlled trial (2014)	No full text available
NCT02538237, The Effect of Sub-gingival Irrigation With Ibuprofen 2% Mouthwash in Treatment of Periodontal Diseases (2015)	No full text available
Flemmig TF, Rumetsch M, Klaiber B. Efficacy of systemically administered acetylsalicylic acid plus scaling on periodontal health and elastase-alpha 1-proteinase inhibitor in gingival crevicular fluid. *J Clin Periodontol*. 1996; 23(3 Pt 1):153–159. doi:10.1111/j.1600-051x.1996.tb02070.x	Not addressing research question
Ng VW, Bissada NF. Clinical evaluation of systemic doxycycline and ibuprofen administration as an adjunctive treatment for adult periodontitis. *J Periodontol*. 1998; 69(7):772–776. doi:10.1902/jop.1998.69.7.772	Not addressing research question
Pinho Mde N, Pereira LB, de Souza SL, et al. Short-term effect of COX-2 selective inhibitor as an adjunct for the treatment of periodontal disease: a clinical double-blind study in humans. *Braz Dent J*. 2008; 19(4):323–328. doi:10.1590/s0103-64402008000400007	Not addressing research question; study design
Taiyeb Ali TB, Waite IM. The effect of systemic ibuprofen on gingival inflammation in humans. *J Clin Periodontol*. 1993; 20(10):723–728. doi:10.1111/j.1600-051x.1993.tb00697.x	Not addressing research question
Shiloah J, Bland PS, Scarbecz M, Patters MR, Stein SH, Tipton DA. The effect of long-term aspirin intake on the outcome of non-surgical periodontal therapy in smokers: a double-blind, randomized pilot study. *J Periodontal Res*. 2014; 49(1):102–109. doi:10.1111/jre.12085	No original data; Pilot study

Appendix C

Table A3. Quality assessment via the Oxford quality scoring system.

	Aras, H. et al., 2007	Azoubel, M.C. et al., 2008	Buduneli, N. et al., 2010	Flemmig, T.F. et al., 1996	Kurtis, B. et al., 2007	Ng, V.W. et al., 1998	Özgören, O. et al., 2014	Pinho Mde, N. et al., 2008	Shiloah, J. et al., 2014	Taiyeb Ali T.B. et al., 1993	Vardar, S. et al., 2003	Yen, C.A. et al., 2008
Described as randomized *	1	1	1	1/split mouth	0	1/split mouth	1	1/split mouth	1	1/split mouth	1	1
Described as double-blind *	0	1	1	1	0	0	1	1	1	0	1	1
Randomization method described and appropriate **	1	1	1	0	0	0	1	0	1	0	0	1
Double-blinding method described and appropriate **	0	0	0	0	0	0	0	1	0	0	0	1
Description of dropouts and withdrawals *	1	1	1	1	0	1	0	1	1	0	0	1
SCORE	3	4	4	3	0	2	3	4	4	1	2	5

* A study receives a score of 1 for "yes" and 0 for "no". ** A study receives a score of 0 if no description is given, 1 if the method is described and appropriate, −1 if the method is described is inappropriate.

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